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Clinical Outcomes and Safety of Patients Treated with NAb-Paclitaxel Plus Gemcitabine in Metastatic Pancreatic Cancer: the NAPA Study

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Abstract

Background: The phase III MPACT trial demonstrated the superiority of gemcitabine (Gem) combined with Nab-paclitaxel (Nab-P) versus gemcitabine alone in previously untreated pa- tients with metastatic pancreatic ductal adenocarcinoma (PDAC). The purpose of this study was to evaluate the effect of Gem/Nab-P in routine clinical practice. Methods: From January 2015 to December 2018, patients with metastatic PDAC receiving first- line treatment with a combination of gemcitabine and Nab-paclitaxel were included in a multicen- tre retrospective observational study. Exploratory analyses of efficacy, and prognostic and predic-tive markers, were performed. Results: The cohort comprised 115 patients (median age 65 [range 50-84] years) with good perfor- mance status (ECOG PS 0-1). The median overall survival (OS) was 11 months (95% CI; 9-13) and the median progression-free survival (PFS) was 6 months (95% CI 5-7). Partial response and stable disease were achieved in 44 and 30 patients, respectively, yielding an overall disease control rate (DCR) of 64.3%. Grade 3-4 hematological toxicity frequency was 22.61% for neutropenia, 5.22% for anemia, and 3.48% for thrombocytopenia. Grade 3 asthenia was recorded in 2.61% of pa- tients. No grade 4 non-hematological events were reported. Dose reduction was necessary in 51.3% of the patients.
Conclusion: Our results confirm the efficacy and safety of a first-line regimen comprising gemc- itabine and Nab-paclitaxel in metastatic PDAC in a real-life population.

Keywords: Metastatic pancreatic adenocarcinoma, combined chemotherapy, nab-paclitaxel, gemcitabine, prognostic factor, cancer.

1. BACKGROUND

Pancreatic adenocarcinoma represents the fourth leading cause of cancer-related deaths in Europe and the United States [1, 2]. It is an aggressive disease characterized by a very poor prognosis leading to a median overall survival (OS) of less than 18 months and a five-year OS rate below 8% [3]. To date, surgery is the only curative treatment avail- able, but this is limited to 20% of patients with respectable disease at the time of diagnosis and is often invalidated by re- currences. Bearing in mind the scarce initial symptomatolo- gy, most patients are diagnosed with locally advanced or me- tastatic disease, limiting the therapeutic approach to sys- temic chemotherapy [4] which has been associated with an improvement in disease-related symptoms and OS relative to the best supportive care [5]. Since 1997, based on pivotal trial results, single-agent gemcitabine has become the first-line standard of care in me- tastatic disease [5]. Subsequently, gemcitabine-based che- motherapy regimens have been compared with gemcitabine alone and, despite the higher response rates, have not im- proved OS significantly due to increased toxicity [5-9]. Recently, two effective regimens have been introduced based on the results of large-scale clinical trials. The first, the FOLFIRINOX regimen, (*i.e.,* 5-FU/leucovorin, irinote- can, and oxaliplatin), was introduced by the PRODIGE 4/ACCORD II trial which compared FOLFIRINOX with gemcitabine alone [10]. FOLFIRINOX treatment was shown to improve progression-free survival (PFS) and OS, respec- tively by 6.4 and 11 months, compared with 3.3 and 6.8 months obtained with gemcitabine. Due to the higher toxici- ty rate compared to gemcitabine, FOLFIRINOX is consid- ered the preferred regimen for patients with metastatic pan- creatic cancer and good performance status (PS) as well as normal organ functions [10]. Moreover, a second regimen with gemcitabine and Nab-- paclitaxel (Gem/Nab-P) has been introduced through a larg- er randomized phase 3 trial (MPACT), demonstrating the su- periority of the combination regimen over gemcitabine alone in previously untreated patients with metastatic pancreatic adenocarcinoma [11]. The median PFS was 5.5 months and OS was 8.5 months in the Gem/Nab-P group, compared to 3.7 and 6.7 months in the gemcitabine group, respectively. Thus, the combination of gemcitabine and Nab-Paclitaxel has been established as another standard first-line treatment for metastatic pancreatic cancer [11]. The most common seri- ous adverse events reported with the combination therapy were neutropenia, fatigue and neuropathy. Currently, FOLFIRINOX and Gem/Nab-P are recom- mended as the first-line regimens for metastatic pancreatic cancer; FOLFIRINOX is the option of choice in younger pa- tients with good PS, but whether the combination is superior to Gem/Nab-P in advanced pancreatic cancer has not yet been clarified [12, 13]. The strict enrolment criteria and sev- eral intrinsic limitations related to randomized clinical trial protocols mean that the samples enrolled in trials to date have not been representative of the population in clinical practice. Phase IV studies on Gem/Nab-P treatment have not yet been performed. The aim of this retrospective study is to evaluate the effectiveness and safety of gemcitabine and Nab-paclitaxel treatment for metastatic pancreatic cancer in a real-world setting.

2. METHODS

2.1. Study Population

Patients with metastatic pancreatic ductal adenocarcino- ma (PDAC), receiving first-line treatment with a combina- tion of gemcitabine and Nab-paclitaxel from January 2015 to December 2018, were considered eligible for our retro- spective analysis. Inclusion criteria were the following: age ≥18 years; his- topathologically confirmed PDAC; Eastern Cooperative On- cology Group performance status (ECOG-PS) 0-1, adequate hematological function (neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥ 9 g/dl); no hepatic or renal impairments. Patients with locally advanced cancer, patients who re- ceived previous chemotherapy treatment or histology other than PDAC were excluded. Written informed consent was obtained from each patient before starting treatment. This study was approved by the *Comitato Etico Regionale* for clinical experimentation of Toscana region (Italy) *area vasta centro* section, number:14565_oss treatment in accordance with the Declaration of Helsinki.

2.2. Treatment Schedule

The initial dose of Gem/Nab-P was chosen according to a previous phase III study (MPACT): 30-40 minutes of intra- venous infusion of Nab-paclitaxel 125 mg/m^2, followed by 30 minutes of gemcitabine 1000 mg/m^2 diluted with 250 ml of saline solution administered intravenously on days 1, 8 and 15 every 4 weeks [11]. Dexamethasone 8mg and On- dansetron 8mg Slow bolus/15 min infusion and ranitidine 50mg Intravenous Slow bolus were used as premedication to start chemotherapy. Recombinant human granulocyte colony-stimulating factor and erythropoietin were adminis- tered as needed. Treatment was modified depending on physician/patient choice, and treatment was continued until disease progression or unacceptable toxicity.

2.3. Assessment

Tumor response evaluation was performed every 3 months by spiral computed tomography (CT). Disease pro- gression was assessed as either radiological or clinical pro- gression. The best response during Gem/Nab-P treatment was radiologically evaluated according to the Response Eval- uation Criteria in Solid Tumour (RECIST) version 1.1 [14]. Blood tests were performed at baseline and every thera- py cycle, while measurement of the carbohydrate antigen (CA)19-9 serum level was performed at baseline and every 12 weeks. Efficacy has been evaluated as OS and PFS. Adverse events during Gem/Nab-P treatment were moni- tored by investigators and reported in clinical charts. Treat- ment-related Adverse Events (AEs) were assessed using the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0 [15]. Variables assessed for prognostic correlations included age ≥70 years, sex, ECOG-PS, primary tumor site, baseline CA19-9 level ≥ 659 × ULN, number of metastatic sites, basal levels of LDH, Gamma-GT, and ALP (calculated as the absolute neutrophil count divided by the absolute lym- phocyte count measured in × 10^3/ml), previous surgery, radia- tion therapy, and biliary stent implantation. In the event of unacceptable toxicity, doses could be re- duced up to two times *per* therapeutic agent (to 100 or 75 mg/m^2 for *Nab-*

P and to 800 or 600 mg/m^2 for gemcitabine). A missing dose within four days of the scheduled administra- tion was considered a dose delay.

2.4. Clinical Outcomes

The primary endpoints were OS and a PFS. The se- condary endpoints were disease control rate (DCR) as well as the rate and severity of treatment-related AEs. Overall sur- vival was defined as the time from the diagnosis of ad-vanced pancreatic cancer to death from any cause or the date of the last follow-up visit. Progression-free survival was defined as the time from the initial assessment at the cancer center to the date of the disease progression, as reported by the clinician. Disease control rate was defined as the propor- tion of patients with the best overall response determined as complete response (CR), partial response (PR) or stable dis- ease (SD). No CR was recorded in our sample.

Table 1. Patient characteristics.

-	**All Patients (N=115)**
Age, years Median Range ≥70	65 50-84 38 (33%)
ECOG PS 1	53 (46.1) 62 (53.9%)
Sex Male Female	61 (53%) 54 (47%)
Site of metastatic disease Liver Lung Peritoneum Others	64 (55.6%) 28 (24.3%) 16 (13.9%) 11 (9.6%)
Number of metastatic sites 1–2 ≥3	69 (60%) 46 (40%)
Carbohydrate antigen 19-9 — U/ml¶ Median Range LDH Median Range GAMMA-GT Median Range ALP Median Range	 659 0.8-182922 163.5 98-710 72 12-1119 112 19-1168
Previous treatment Radiation Therapy Surgery Biliary stent	10 (8.7%) 28 (24.3%) 38 (33%)
Lines of treatment for metastatic disease 2 >2	47 (40.9%) 15 (13%)
Pain Yes	48 (41.7%)

2.5. Statistical Analysis

All patients were included in the statistical analysis. De- scriptive statistics were carried out on the clinical parame- ters of the PC. Time-dependent outcomes were estimated us- ing the Kaplan-Meier method and compared, at univariate analysis, using the log-rank test. Parameters with a statistical- ly significant log-rank test were considered independent vari- ables and included in the multivariate Cox proportional hazard regression linear model to compare hazard ratio (HR) and 95% confidence interval (95% CI). A two-sided p-value < 0.05 was considered statistically significant. STATA v.2012 was used for statistical analysis.

3. RESULTS

3.1. Study Population

Overall, from January 2015 to December 2018, 143 pa- tients with metastatic pancreatic cancer treated with Gem/N- ab-P have been identified. Among them, 29 patients were ex- cluded based on the exclusion criteria. Thus, a sample of 115 patients has been used for efficacy and safety analysis. Patients' characteristics are described in Table **1**. The me- dian age was 65 years (range 50-84) with a male: female ra- tio 61:54. ECOG-PS was 0 in 46.1% of patients and one in 53.9%. The most frequent metastatic sites were liver (56%), lung (24.3%), and peritoneum (13.9%); 69% of patients had 1-2 metastatic sites, and 40%

had three or more. Radiation therapy has been performed in 8.7% of the cohort, whereas 24.3% and 33% have been treated with surgery and biliary stent, respectively. None of the patients has received previ- ous chemotherapy. Median baseline CA 19.9 was 659 U/ml (range 0.8-182,922 U/ml). Forty-eight (41.7%) patients re- ported cancer-related pain or other disease-related symp- toms before treatment. Our population study presented with comorbidities: the most frequent was cardiovascular 48 (41.7%) (Table **1S**), and 37 (32.2%) patients presented with >1 comorbidity.

3.2. Treatment

During the study, patients received a median of five cy- cles (range 1–17) of treatment with a starting dose of *Nab*-P 125 mg/m^2 plus Gem 1,000 mg/m^2. Dose reduction was ne- cessary for 59 (51.3%) patients without significant differ- ence between gemcitabine and Nab-paclitaxel; 63 (54.8%) required only one dose reduction, whereas 32 (27.8%) had two dose reductions. Dose delays and treatment interruption occurred in 43 (37.4%) and 44 (38.4%) patients, respective- ly. Neutropenia, peripheral neuropathy, and asthenia were the main cause of dose reductions, delays or stopping treat- ment.

3.3. Efficacy

Overall, the median follow-up period was 10 (range 1-54) months. The median OS was 11 months (95% CI; 9-13) and the median PFS was 6 months (95% CI 5–7). Par- tial response and stable disease were recorded in 44 and 30 patients, respectively, yielding an overall DCR of 64.3% (Table **2**). For 9 (7.8%) patients, the response was not evalu- able. Regarding survival, univariate analysis showed that age, ECOG-PS 1, Ca 19.9 U/ml ≥ 659 U/ml and number of me- tastatic sites ≥ 3 were negatively correlated with OS. In fact, OS was statistically lower according to age (9 *vs*. 13 months, p = 0.002, Fig. **1**); ECOG-PS (10 *vs*. 13 months, p =0.04, Fig. **1**); Ca 19.9 (10 *vs.* 14 months, p = 0.01, Fig. **1**) number of metastatic sites (8 *vs*. 13 months, p = <0.001, Fig.**1**). Conversely, previous surgery, cycles of Gem/Nab-P >4 and more than one line of treatment for metastatic disease were correlated with a better OS that was statistically higher according to previous surgery (13 *vs*. 10 months, p = 0.03, Fig. **2**); cycles of Gem/Nab-P (14 *vs.* 6 months, p = <0.001,Fig. **2**); and lines of treatment (13 *vs*. 9 months, p = 0.01, Fig. **2**). Other variables examined did not show statistically significant effects (Table **3**). Multivariate analysis has con- firmed metastatic sites ≥ 3 (HR 1.68; 95% CI 1.15–3.15; $p = 0.04$) and CA 19.9 levels ≥ 659 U/ml (HR 1.84; 95% CI 1.19–2.82; $p = 0.006$) were correlated with a worse OS (Table **4**). On the other hand, previous surgery (HR 0.31; 95% CI 0.17–0.55; $p = 0.001$), cycles of Gem/Nab-P > 4 (HR 0.21; 95% CI 0.13–0.35; $p = 0.001$), and lines of treat- ment for metastatic disease >1 (HR 0.47; 95% CI 0.30–0.73; $p = 0.001$), were correlated with a better overall survival (Table **4**).

Table 2. The best response, PFS, and OS according to neutrope- nia grade.

	All Patients (N=115)
PR	44 (38.3%)
SD	30 (26.1%)
DCR (PR + SD)	74 (64.3%)
PD	32 (27.8%)
NE	9 (7.8%)
PFS M-months (95% IC)	6 (5-7)
OS M-months 95% IC	11 (9-13)
Cycles	
Median	5
Range	1-17
GCF-Prophylaxis	25 (21.9)%)

Number (N), partial response (PR), stable disease (SD), disease control rate (DCR), progression disease (PD), not evaluable (NE); Median (median); progression free survi- val (PFS); overall survival (OS).

Regarding progression-free survival, univariate analysis showed that the number of metastatic sites ≥ 3, the baseline level of CA 19.9 U/ml ≥ 659 U/ml, and pain were negatively correlated with PSF (Table **3**). Multivariate analysis has con- firmed the number of metastatic sites ≥ 3 (HR 2.73; 95% CI 1.41–5.27; $p = 0.003$) and CA 19.9 levels ≥ 659 U/ml (HR 1.67; 95% CI 1.08–2.57; $p = 0.02$) as an independent, nega- tive and prognostic indicators for PFS, respectively (Table **4**).

3.4. Safety

Hematological and non-hematological adverse event fre- quencies are shown in Table **5**. Overall, the treatment was well-tolerated, and most non-hematological toxicities were reported as grade 1 or 2. In our cohort, the frequency of grade 3 bone marrow toxicity was 15.56% for neutropenia, 2.61% for anemia, and 2.61% for thrombocytopenia. Grade 4 hematological toxicity comprised neutropenia in 8 patients (6.96%), anemia in 3 (2.61%), and thrombocytopenia in 1 (0.87%). The only grade 3 non-hematological toxicity was asthenia recorded in 3 patients (2.61%). No grade 4 non-he- matological events were reported.

4. DISCUSSION

Our Italian retrospective study seems to confirm the treat- ment benefit of Gem/Nab-P treatment in patients with me- tastatic pancreatic cancer in a real-world setting, according to the result of the randomized phase III MPACT trial [11]. Several factors, including small sample size and differ- ences in inclusion/exclusion criteria, meant that a direct com- parison between the pivotal MPACT trial and this real-- world experience was not fully possible. However, despite the limitations, we were able to confirm that the combina- tion regimen with Gem/Nab-P was effective and safe in our population compared with the randomized controlled trial sample. Specifically, we observed 11 months median OS and 6 months median PFS with a DCR of 64.3%. When comparing our results with those of the pivotal trial, there are some differences in patients' characteristics that we need to consider. In the MPACT trial, patients were younger, with approximatively 60% of the participants aged below 65, with a Karnofsky Performance Status (KPS) of 100-90% [16]. On the other hand, 33% of patients in our sample were older than 70 years and 46.1% have reported an ECOG-PS 0. Additionally, we treated 32% of patients with >1 concomitant comorbidities (Table **1s**). All these data sup- port the use of Gem/Nab-P in a "real-life" population of elderly patients with varying comorbidities. Recent retrospective studies in patients with both me- tastatic and locally advanced disease have reported a differ- ence in efficacy data between metastatic and locally ad- vanced subgroups. For example, Wang *et al.* achieved an OS of 10.5 months in the total cohort and similar survival of 10 months in the metastatic subgroup [21]. Recently, Bloms- trand *et al.* observed a trend towards better prognosis in the locally advanced group of 22 patients. PFS and OS were 6.8 and 17.1 months, respectively in the locally advanced group, compared to 4.5 and 9.4 months in the metastatic group of 53 patients, although the differences reported were not statis- tically significant [22]. In another multicentre retrospective study on elderly patients, PFS and OS were 12.1 and 21.8 months in 42 patients with locally advanced cancer and 5.9 and 13.3 months in 59 patients with metastasis, respectively [23]. In our study, according to the MPCT trial, we have en- rolled only chemo-naïve patients with upfront metastatic dis- ease. Unfortunately, subgroup analysis on metastatic burden has shown a worse prognosis for patients with three or more metastases, a difference statistically significant in relation to OS (HR 1.68; 95% CI 1.15–3.15; $p = 0.04$) and PFS (HR 2,73; 95% CI 1.41–5,27; $p = 0.003$), suggesting the main role of tumor burden as a prognostic factor in metastatic pan- creatic cancer. Several investigators have reported their experience with Gem/Nab-P in clinical practice in patients with locally ad- vanced and metastatic pancreatic cancer, based on retrospec- tive studies. De Vita and colleagues have reported a median PFS and OS of 6.7 and 10 months, respectively, enrolling a cohort of 41 patients [17]. Lo Re *et al.* , in a smaller previ- ous study with 37 patients, have achieved a median PFS of

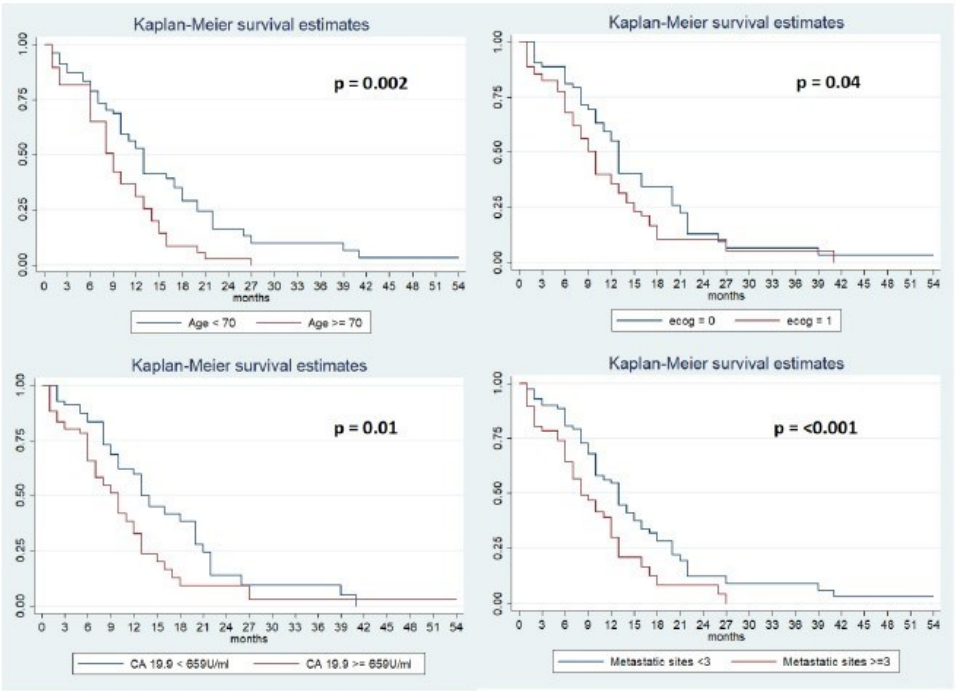

Fig. (1). Overall survival of Gem/Nab-P according to different prognostic factors: age, ECOG, CA 19.9, and metastatic sites. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*.)

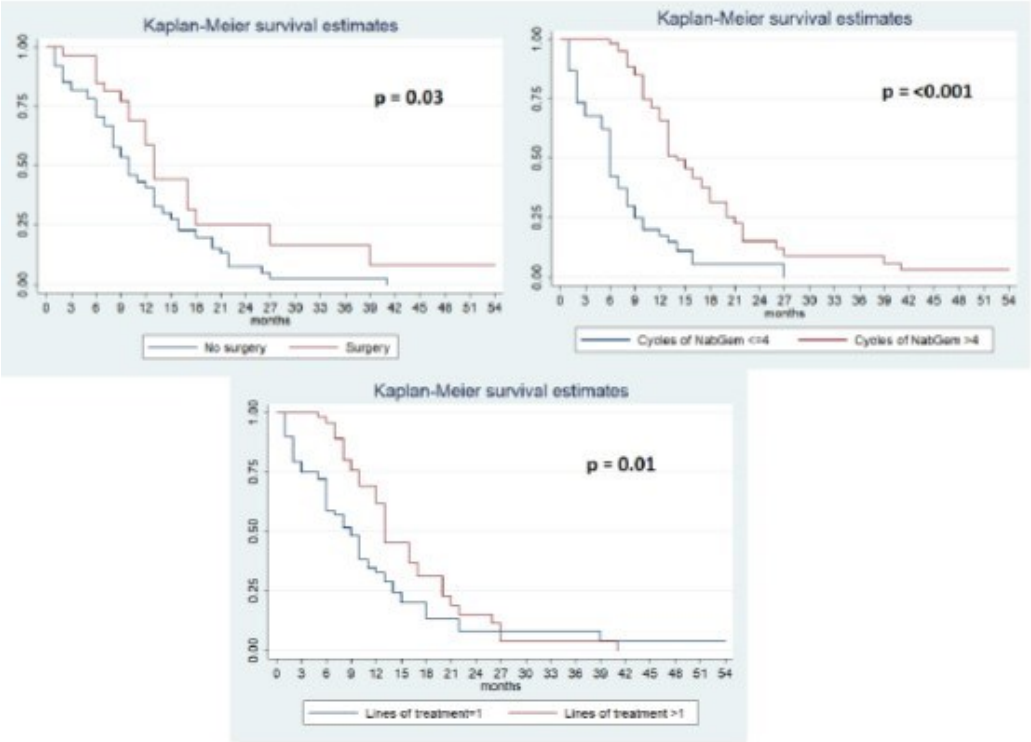

Fig. (2). Overall Survival of Gem/Nab-P according to different prognostic factors: surgery, cycles of therapy, and lines of treatment. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*.)

Table 3. Univariate analysis for PFS and OS.

	HR	IC 95%	P
Progression free Survival			
Age ≥70	1.44	0.93-2.24	0.1
ECOG PS (1 vs 0)	1.17	0.78-1.77	0.4
Sex (male vs female)	1.08	0.71-1.64	0.7
N. of metastatic sites ≥3	3.85	2.06-7.20	0.001
Carbohydrate antigen 19-9 ≥ 659U/ml	1.86	1.23-2.83	0.003
Previous Radiation Therapy	0.63	0.29-1.37	0.2
Previous Surgery	0.76	0.47-1.26	0.2
Previous Biliary stent	0.75	0.48-1.17	0.2
Pain present	1.51	1-2.31	0.05
LDH ≥ 163.5 U/ml	0.80	0.51-1.25	0.3
Gamma-gt ≥ 72 U/ml	1.02	0.68-153	0.9
ALP ≥ 112 U/ml	0.98	0.66-1.50	0.9
Overall Survival			
Age ≥70	1.88	1.23-2.89	0.004
ECOG PS (1 vs 0)	1.52	1-2.31	0.05
Sex (male vs female)	1.20	0.79-1.83	0.4
N. of metastatic sites ≥3	3.91	2-7.63	<0.001
Carbohydrate antigen 19-9 ≥ 659U/ml	1.71	1.22-2.60	0.01
Previous Radiation Therapy	0.47	0.19-1.16	0.1
Previous Surgery	0.58	0.35-0.99	0.04
Previous Biliary stent	0.84	0.54-1,32	0.4
Pain present	1.50	0.98-2.29	0.06
LDH ≥ 163.5 U/ml	0.77	0.47-1.24	0.3
Gamma-gt ≥ 72 U/ml	1.08	0.71-1.65	0.7
ALP ≥ 112 U/ml	0.96	0.63-1.44	0.8
Cycles of NabGem >4	0.28	0.18-0.44	0.001
Lines of treatment for metastatic disease>1	0.60	0.39-0.91	0.01

5.5 and OS of 12.1 months [18]. Montes *et al.* recorded in a sample of 39 patients slightly longer PFS and OS (9 and 15 months, respectively), different from the study of Nea Papne- ja *et al.* that reported, in a cohort of 33 patients, a shorter PFS and OS of 4 and 9 months, respectively [19, 20]. Com- pared with all these studies, we evaluated a greater number of patients from different institutions, confirming the effica- cy of Gem/Nab-P as a first-line treatment for metastatic pan- creatic cancer. No standard second-line treatment following the failure of first-line chemotherapy has been available to date, and questions related to treatment choice and sequence are ongo- ing. However, second-line chemotherapy produced a survi- val benefit when compared with best supportive care and was found to be more effective in patients with early progression within 3 months after first-line treatment [24-26]. In our study, an increased OS was recorded in patients with two or more treatment lines for metastatic disease (HR 0.47; 95% CI 0.30–0.73; $p = 0.001$), supporting the role of a se- cond or further line of treatment as prognostic of survival for metastatic pancreatic cancer. To note, the safety profile in our study was better com- pared to the pivotal trial and other previous studies [11, 18, 19, 28]. Adverse non-hematological events were generally of grade 2 or 1; no grade 3 or 4 peripheral neurotoxicity was observed in our cohort. Grade 3 asthenia was reported in 2.61% of patients, in contrast with data of the MPACT study (17%). Grade 3 or 4 hematological toxicity was observed in a lower percentage than the pivotal trial, consistent with the data reported in the previous studies in clinical practice [17, 18, 22, 23].

Table 4. Multivariate analysis for PFS and OS.

	HR	IC 95%	P
Progression-free Survival			
N. of metastatic sites ≥3	2.73	1.41-5.27	0.003
Carbohydrate antigen 19-9 ≥ 659U/ml	1.67	1.08-2.57	0.02
Pain present	1.30	0.84-2.01	0.23
Overall Survival			
Age ≥70	1.18	0.74-1.87	0.5
ECOG PS (1 vs 0)	1.05	0.69-1.67	0.8
N. of metastatic sites ≥3	1.68	1.15-3.15	0.04
Carbohydrate antigen 19-9 ≥ 659U/ml	1.84	1.19-2.82	0.006
Previous Surgery	0.31	0.17-0.55	0.001
Cycles of NabGem >4	0.21	0.13-0.35	0.001
Lines of treatment for metastatic disease >1	0.47	0.30-0.73	0.001

Table 5. Summary of most ≥3 adverse events for NabGem.

	Grade 3	Grade 4
Hematological		
Neutropenia	18 (15.65%)	8 (6.96%)
Anemia	3 (2.61%)	3 (2.61%)
Thrombocytopenia	3 (2.61%)	1 (0.87%)
Non-Hematological	15* (13.04%)	13** (11.30%)
Neuropathy	14* (12.17%)	7** (6.09%)
Diarrhea	3 (2.61%)	
Asthenia		

*Grade 1; ** Grade 2

Overall, the regimen was well tolerated, in line with pre- vious studies, although some patients required dose reduc- tion or treatment discontinuation. Based on a retrospective analysis of the MPACT trial, the dose reduction and/or de- lay of chemotherapeutic drugs to manage toxicities can be carried out with no reductions in the efficacy of the estab- lished starting dose [29]. Among other prognostic factors related to PFS and OS, we found that baseline CA 19.9 value ≥ 659 U/ml was linked to a worse OS. In line with these data, several studies retrospectively investigated the prognostic role of basal CA19.9 during first-line chemotherapy [30]. The role of CA 19.9 in pancreatic cancer is well established, National Com- prehensive Cancer Network (NCCN] guidelines for pancreat- ic cancer recommends CA19.9 as the only biomarker of dis- ease; in fact, CA 19.9 is strongly correlated with tumor bur- den [30]. Nonetheless, the optimal level of CA 19.9 as a prognostic factor remains uncertain, because while we found a value of 659 U/ml, other studies found both higher than lower values. Future prospective studies are awaited to define the best basal value of CA 19.9 as a predictor of survi- val during first-line Gem/Nab-P. In addition, we also found >4 cycles of therapy to be an independent positive prognostic factor associated with OS. In this context, Lo Re *et al.* [18] confirmed a longer OS for patients treated with ≥ 4 cycles of Gem/Nab-P. Although it might be intuitive that more cycles of therapy would corre- late with a longer OS, it is worth noting that 6 cycles of Gem/Nab-P therapy are typical in order to try to avoid exces- sive toxicity. The optimal duration of Gem/Nab-P therapy therefore requires further investigation. Furthermore, >1 lines of treatment for metastatic disease correlated with a bet- ter OS (we will describe the role of second-line therapy after Gem/Nab-P therapy in a separate paper). Finally, no statisti- cally significant correlation between OS and ECOG-PS was highlighted, contrasting with Lo Re *et al.* [18] who reported a correlation between PS <2 and a higher number of therapy cycles, allowing an increase in OS, supporting no efficacy of Gem/Nab-P for patients with PS=2. Our study has some limitations mainly owing to its retro- spective nature. The largest sample compared to that of pre- vious studies, and the enrolment of only metastatic patients, represent strengths aimed at increasing knowledge about the efficacy and safety of Gem/Nab-P in patients with stage IV disease.

CONCLUSION

Progress has recently been made in the first-line of che- motherapy in locally advanced and metastasized pancreatic cancer. Studies of further lines of therapy are ongoing. In the absence of randomized control trials, the choice of the first-line chemotherapy between Gem/Nab-P and FOLFIRI-

NOX in patients with metastatic pancreatic cancer is mainly based on careful patient selection, their performance status, comorbidity, and medical preference. Our study confirms the activity, efficacy, and safety of gemcitabine plus Nab-P as a first-line regimen, in a large group of patients with ex- clusive metastatic pancreatic cancer, in a real-world setting. Despite clinical efficacy and the overall good tolerance of therapy, the identification of serum or tissue markers could allow a personalized and even better-tolerated treatment.

REFERENCES

[1]Maisonneuve, P. Epidemiology and burden of pancreatic cancer.*Presse Med.,* **2019**, *48*(3 Pt 2), e113-e123.http://dx.doi.org/10.1016/j.lpm.2019.02.030 PMID: 30878335

[2] Ferlay, J.; Colombet, M.; Soerjomataram, I.; Dyba, T.; Randi, G.;Bettio, M.; Gavin, A.; Visser, O.; Bray, F. Cancer incidence andmortality patterns in Europe: Estimates for 40 countries and 25 majorcancers in 2018. *Eur. J. Cancer,* **2018**, *103*, 356-387.http://dx.doi.org/10.1016/j.ejca.2018.07.005 PMID: 30100160

[3] Bilimoria, K.Y.; Bentrem, D.J.; Ko, C.Y.; Ritchey, J.; Stewart,A.K.; Winchester, D.P.; Talamonti, M.S. Validation of the 6th editionAJCC Pancreatic Cancer Staging System: report from the NationalCancer Database. *Cancer,* **2007**, *110*(4), 738-744.http://dx.doi.org/10.1002/cncr.22852 PMID: 17580363

[4] Vincent, A.; Herman, J.; Schulick, R.; Hruban, R.H.; Goggins, M. Pancreatic cancer. *Lancet,* **2011**, *378*(9791), 607-620.http://dx.doi.org/10.1016/S0140-6736(10)62307-0 PMID:21620466

[5] Burris, H.A., III; Moore, M.J.; Andersen, J.; Green, M.R.; Rothenberg,M.L.; Modiano, M.R.; Cripps, M.C.; Portenoy, R.K.; Storniolo,A.M.; Tarassoff, P.; elson, R.; Dorr, F.A.; Stephens, C.D.;Von Hoff, D.D. Improvements in survival and clinical benefitwith gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.,* **1997**, *15*(6),2403-2413.http://dx.doi.org/10.1200/JCO.1997.15.6.2403 PMID: 9196156

[6] Rocha Lima, C.M.; Green, M.R.; Rotche, R.; Miller, W.H., Jr; Jeffrey,G.M.; Cisar, L.A.; Morganti, A.; Orlando, N.; Gruia, G.;Miller, L.L. Irinotecan plus emcitabine results in no survival advantagecompared with gemcitabine monotherapy in patients withlocally advanced or metastatic pancreatic cancer despite increasedtumor response rate. *J. Clin. Oncol.,* **2004**, *22*(18), 3776-3783.http://dx.doi.org/10.1200/JCO.2004.12.082 PMID: 15365074

[7] Sultana, A.; Smith, C.T.; Cunningham, D.; Starling, N.; Neoptolemos,J.P.; Ghaneh, P. Meta-analyses of chemotherapy for locallyadvanced and metastatic pancreatic cancer. *J. Clin. Oncol.,* **2007**,*25*(18), 2607-2615.http://dx.doi.org/10.1200/JCO.2006.09.2551 PMID: 17577041

[8] Heinemann, V.; Quietzsch, D.; Gieseler, F.; Gonnermann, M.;Schönekäs, H.; Rost, A.; Neuhaus, H.; Haag, C.; Clemens, M.;Heinrich, B.; Vehling-Kaiser, U.; Fuchs, M.; Fleckenstein, D.; Gesierich,W.; Uthgenannt, D.; Einsele, H.; Holstege, A.; Hinke, A.;Schalhorn, A.; Wilkowski, R. Randomized phase III trial of gemcitabineplus cisplatin compared with gemcitabine alone in advancedpancreatic cancer. *J. Clin. Oncol.,* **2006**, *24*(24),3946-3952.http://dx.doi.org/10.1200/JCO.2005.05.1490 PMID: 16921047

[9] Kindler, H.L.; Niedzwiecki, D.; Hollis, D.; Sutherland, S.; Schrag,D.; Hurwitz, H.; Innocenti, F.; Mulcahy, M.F.; O'Reilly, E.; Wozniak,T.F.; Picus, J.; hargava, P.; Mayer, R.J.; Schilsky, R.L.;Goldberg, R.M. Gemcitabine plus bevacizumab compared withgemcitabine plus placebo in patients with advanced pancreatic cancer:phase III trial of the Cancer and Leukemia Group B (CALGB80303). *J. Clin. Oncol.,* **2010**, *28*(22), 3617-3622.http://dx.doi.org/10.1200/JCO.2010.28.1386 PMID: 20606091

[10] Conroy, T.; Desseigne, F.; Ychou, M.; Bouché, O.; Guimbaud, R.;Bécouarn, Y.; Adenis, A.; Raoul, J.L.; Gourgou-Bourgade, S.; dela Fouchardière, C.; Bennouna, J.; Bachet, J.B.; Khemissa-Akouz,F.; Péré-Vergé, D.; Delbaldo, C.; Assenat, E.; Chauffert, B.;Michel, P.; Montoto-Grillot, C.; Ducreux, M. Groupe Tumeurs Digestivesof Unicancer; PRODIGE Intergroup. FOLFIRINOX versusgemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.,***2011**, *364*(19), 1817-1825.http://dx.doi.org/10.1056/NEJMoa1011923 PMID: 21561347

[11] Von Hoff, D.D.; Ervin, T.; Arena, F.P.; Chiorean, E.G.; Infante,J.; Moore, M.; Seay, T.; Tjulandin, S.A.; Ma, W.W.; Saleh, M.N.;Harris, M.; Reni, M.; Dowden, S.; Laheru, D.; Bahary, N.; Ramanathan,R.K.; Tabernero, J.; Hidalgo, M.; Goldstein, D.; Van Cutsem,E.; Wei, X.; Iglesias, J.; Renschler, M.F. Increased survivalin pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl.J. Med.,* **2013**, *369*(18), 1691-1703.http://dx.doi.org/10.1056/NEJMoa1304369 PMID: 24131140

[12] Sohal, D.P.S.; Mangu, P.B.; Khorana, A.A.; Shah, M.A.; Philip,P.A.; O'Reilly, E.M.; Uronis, H.E.; Ramanathan, R.K.; Crane,C.H.; Engebretson, A.;Ruggiero, J.T.; Copur, M.S.; Lau, M.; Urba,S.; Laheru, D. Metastatic pancreatic cancer: American Societyof Clinical Oncology clinical practice guideline. *J. Clin. Oncol.,* **2016**, *34*(23), 2784-2796.http://dx.doi.org/10.1200/JCO.2016.67.1412 PMID: 27247222

[13] Panel NP adenocarcinoma. NCCN Guidelines Pancreatic Adenocarcinoma*Gastrointest Oncol,* **2019**.www.nccn.org

[14] Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent,D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney,M.; Rubinstein, L.; Shankar, L.; Dodd, L.; Kaplan, R.; Lacombe,D.; Verweij, J. New response evaluation criteria in solid tumours:revised RECIST guideline (version 1.1). *Eur. J. Cancer,* **2009**, *45*(2), 228-247.http://dx.doi.org/10.1016/j.ejca.2008.10.026 PMID: 19097774

[15]National Cancer Institute. Common Terminology Criteria for AdverseEvents (CTCAE) version 4.0. NIH Publ **2009**.ctep.cancer.-gov

[16] Frese, K.K.; Neesse, A.; Cook, N.; Bapiro, T.E.; Lolkema, M.P.;Jodrell, D.I.; Tuveson, D.A. nab-Paclitaxel potentiates gemcitabineactivity by reducing cytidine deaminase levels in a mousemodel of pancreatic cancer. *Cancer Discov.,* **2012**, *2*(3), 260-269.http://dx.doi.org/10.1158/2159-8290.CD-11-0242 PMID: 22585996

[17] De Vita, F.; Ventriglia, J.; Febbraro, A.; Laterza, M.M.; Fabozzi,A.; Savastano, B.; Petrillo, A.; Diana, A.; Giordano, G.; Troiani,T.; Conzo, G.; Galizia, G.; Ciardiello, F.; Orditura, M. NAB-paclitaxeland gemcitabine in metastatic pancreatic ductal adenocarcinoma(PDAC): from clinical trials to clinical practice. *BMC Cancer,* **2016**, *16*(1), 709.http://dx.doi.org/10.1186/s12885-016-2671-9 PMID: 27590845

[18] Lo Re, G.; Santeufemia, D.A.; Foltran, L.; Bidoli, E.; Basso,S.M.M.; Lumachi, F. Prognostic factors of survival in patientstreated with nab-paclitaxel plus gemcitabine regimen for advancedor metastatic pancreatic cancer: a single institutional experience.*Oncotarget,* **2015**, *6*(10), 8255-8260.http://dx.doi.org/10.18632/oncotarget.3143 PMID: 25779664

[19] Montes, AF; Villarroel, PG; Ayerbes, M; De La Cámara Gómez,J; Aldana, GQ; Tuñas, LV Prognostic and predictive markers of responseto treatment in patients with locally advanced unresectableand metastatic pancreatic adenocarcinoma treated with gemcitabine/nab-paclitaxel: Results of a retrospective analysis *J CancerRes Ther,* **2017**, *13*(2), 240-245.

[20] Papneja, N; Zaidi, A; Chalchal, H; Moser, M; Tan, K; Olson, CComparisons of Outcomes of Real-World Patients With AdvancedPancreatic Cancer Treated With FOLFIRINOX Versus Gemcitabineand Nab-Paclitaxel: A Population-Based Cohort Study *Pancreas,***2019**, *48*(7), 920-926.http://dx.doi.org/10.1097/MPA.0000000000001340

[21] Wang, Y.; Camateros, P.; Cheung, W.Y. A Real-World Comparisonof FOLFIRINOX, Gemcitabine Plus nab-Paclitaxel, andGemcitabine in Advanced ancreatic Cancers. *J. Gastrointest.Cancer,* **2019**, *50*(1), 62-68.http://dx.doi.org/10.1007/s12029-017-0028-5 PMID: 29143916

[22] Blomstrand, H.; Scheibling, U.; Bratthäll, C.; Green, H.; Elander,N.O. Real world evidence on gemcitabine and nab-paclitaxel combinationchemotherapy in advanced pancreatic cancer. *BMCCancer,* **2019**, *19*(1), 40.http://dx.doi.org/10.1186/s12885-018-5244-2 PMID: 30621618

[23] Kobayashi, S.; Ueno, M.; Ikeda, M.; Ozaka, M.; Sano, Y.; Hirotani,A.; Tozuka, Y.; Fukushima, T.; Tezuka, S.; Moriya, S.; Umemoto,K.; Watanabe, K.; Sasaki, M.; Hashimoto, Y.; Imaoka, H.;Ohno, I.; Mitsunaga, S.; Yamada, I.; Sasaki, T.; Sasahira, N.; Morimoto,M. A Multicenter Retrospective Study of GemcitabinePlus Nab-Paclitaxel for Elderly Patients With Advanced PancreaticCancer. *Pancreas,* **2020**, *49*(2), 187-92.http://dx.doi.org/10.1097/MPA.0000000000001484 PMID:32011536

[24] Walker, E.J.; Ko, A.H. Beyond first-line chemotherapy for advancedpancreatic cancer: an expanding array of therapeutic options?*World J. Gastroenterol.,* **2014**, *20*(9), 2224-2236.http://dx.doi.org/10.3748/wjg.v20.i9.2224 PMID: 24605022[25] Oettle, H; Riess, H; Stieler, JM; Heil, G; Schwaner, I; Seraphin, J Second-line oxaliplatin, folinic acid, and fluorouracil versus folinicacid and fluorouracil alone for gemcitabine-refractory pancreaticcancer: Outcomes from the CONKO-003 Trial *J Clin Oncol,***2014**, *32*(23), 2423-9.

[26] Kaddis, N.; Saif, M.W. Second-line treatment for pancreatic cancer.*JOP,* **2014**, *15*(4), 344-347.PMID: 25076339[27] Taieb, J.; Pointet, A.L.; Van Laethem, J.L.; Laquente, B.; Pernot,S.; Lordick, F.; Reni, M. What treatment in 2017 for inoperablepancreatic cancers? *Ann. Oncol.,* **2017**, *28*(7), 1473-1483.http://dx.doi.org/10.1093/annonc/mdx174 PMID: 28459988
[28] Braiteh, F.; Patel, M.B.; Parisi, M.; Ni, Q.; Park, S.; Faria, C. Comparativeeffectiveness and resource utilization of *nab*-paclitaxelplus gemcitabine vs FOLFIRINOX or gemcitabine for the first--line treatment of metastatic pancreatic adenocarcinoma in a UScommunity setting. *Cancer Manag. Res.,* **2017**, *9*, 141-148.http://dx.doi.org/10.2147/CMAR.S126073 PMID: 28461766
[29] Scheithauer, W.; Ramanathan, R.K.; Moore, M.; Macarulla, T.;Goldstein, D.; Hammel, P.; Kunzmann, V.; Liu, H.; McGovern,D.; Romano, A.; Von Hoff, D.D. Dose modification and efficacyof nab-paclitaxel plus gemcitabine vs. gemcitabine for patientswith metastatic pancreatic cancer: phase III MPACT trial. *J. Gastrointest.Oncol.,* **2016**, *7*(3), 469-478.http://dx.doi.org/10.21037/jgo.2016.01.03 PMID: 27284481
[30] Dell'Aquila, E.; Fulgenzi, C.A.M.; Minelli, A.; Citarella, F.; Stellato,M.; Pantano, F.; Russano, M.; Cursano, M.C.; Napolitano, A.; Zeppola, T.; Vincenzi, B.; Tonini, G.; Santini, D. Prognosticand predictive factors in pancreatic cancer. *Oncotarget,* **2020**, *11*(10), 924-941.http://dx.doi.org/10.18632/oncotarget.27518 PMID: 32206189